Arima

Moclobemide

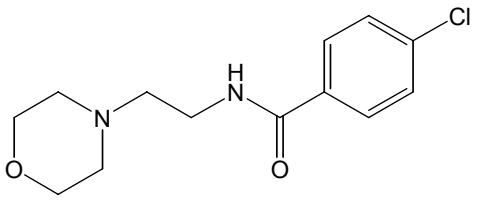
PRODUCT INFORMATION

Name of the Medicine

Active ingredient: Moclobemide

Chemical name: p-chloro-N-(2-morpholinoethyl) benzamide.

The structural formula is:



Molecular formula: $C_{13}H_{17}O_2N_2Cl$ Molecular weight: 268.74.
CAS registry number: 71320-77-9

Description

Moclobemide is a white to slightly reddish crystalline powder. It contains no crystal water and is not hygroscopic. It is soluble in water at 0.4 g/100 mL. The pKa is approximately 6.2.

Each Arima 150 tablet contains 150 mg of moclobemide and is light yellow, film-coated, scored and marked with MOC 150. The tablets also contain lactose, maize starch, povidone, sodium starch glycollate, magnesium stearate, ethylcellulose, macrogol 6000, hypromellose, purified talc, titanium dioxide and iron oxide yellow CI 77492.

Each Arima 300 tablet contains 300 mg of moclobemide and is white to yellowish white, film-coated, scored and marked with MOC 300. The tablets also contain lactose, maize starch, povidone, sodium starch glycollate, magnesium stearate, ethylcellulose, macrogol 6000, hypromellose, purified talc and titanium dioxide.

Pharmacology

Actions

Moclobemide is an antidepressant which affects the monoaminergic cerebral neurotransmitter system by means of a reversible inhibition of monoamine oxidase. There are two types of monoamine oxidases, A and B, which vary in their substrate specificity. Moclobemide is relatively selective for type A. At a 300 mg dose, the inhibition of monoamine oxidase A is approximately 80% while that of monoamine oxidase B is approximately 20-30%. The inhibition is short lasting (approximately 24 hours).

The metabolism of dopamine, noradrenaline and serotonin is decreased by this effect, and this leads to increased extracellular concentrations of these neuronal transmitters. As a result of its elevating effect on mood and psychomotor activity, Arima relieves symptoms such as dysphoria, exhaustion, lack of drive and poor ability to concentrate. These effects most often appear within the first week of therapy. Although Arima has no sedative properties it does increase total sleep time. Arima does not impair alertness or reaction time.

Arima appears to be suitable for ambulatory treatment as it is not sedating and does not impair vigilance or ability to react.

Arima is well tolerated. Short-term and long-term animal studies indicate low toxicity. Little hepatic or cardiac toxicity has been observed. There is a low incidence of raised liver enzymes.

Pharmacokinetics

Absorption
After oral administration, moclobemide is completely absorbed from the gastrointestinal tract into the portal blood. A hepatic first-pass effect reduces the systemically available dose fraction (bioavailability:F). This reduction is more pronounced after single (F: 60%) than after multiple (F: >80%) doses.

Following the administration of a 100 mg single dose of moclobemide to healthy subjects, peak plasma concentrations ranged from 488 ng/mL to 1,450 ng/mL (mean C_{max}: 849 ng/mL) and were reached in 0.5 to 3.5 hours (mean T_{max}: 49 min). During the second week of a 100 mg t.i.d. dosing regimen in healthy subjects, the steady-state trough concentrations of moclobemide ranged between 114 ng/mL and 517 ng/mL. An increase in the dose to 150 mg t.i.d. resulted in a greater than proportional increase in moclobemide steady-state trough concentrations, namely to concentrations ranging between 346 ng/mL and 1,828 ng/mL.

Distribution
Due to its lipophilic nature, moclobemide is extensively distributed in the body with an apparent volume of distribution (V_{ss}) of about 1.2 L/kg. Binding of the drug to plasma proteins, mainly albumin, is relatively low (50%). Peak plasma concentrations of moclobemide increase over the first week of therapy and remain stable thereafter. When the daily dose is increased, there is a more than proportional increase in steady-state concentrations.

Metabolism
Moclobemide is almost entirely metabolised before its elimination from the body. Metabolism occurs largely via oxidative reactions on the morpholine moiety of the molecule. Moclobemide is metabolised in part by the polymorphic isoenzymes CYP2C19 and CYP2D6. Thus in genetically or drug-induced (via metabolic inhibitors) poor metabolisers, metabolism of the drug may be affected. Approximately 2% of the Caucasian population and 15% of the Asian population can be genetically phenotyped as slow metabolisers with respect to oxidative hepatic metabolism. It was found that the area under the curve (AUC) measurement in slow metaboliser subjects was approximately 1.5 times greater than in extensive metaboliser subjects for the same dose of moclobemide. This increase is within the normal range of variation (up to two-fold) typically seen in patients. Two studies conducted to investigate the magnitude of these effects suggested that, due to the presence of multiple alternative metabolic pathways, they are therapeutically unimportant and should not necessitate dosage modifications.

One metabolite, the N-oxide metabolite, has slight pharmacological activity. This and other degradation products with pharmacological activity in-vitro or in animal experiments are present in the systemic circulation in man at very low concentrations only.

Elimination
Moclobemide is rapidly eliminated from the body. Less than 1% of a dose is excreted renally unchanged. The metabolites formed are eliminated renally.

Blood clearance is approximately 20-50 L/hr, the average elimination half life is two hours with a slight increase at increased doses.

Multiple dose studies in the elderly and in patients with renal insufficiency suggest no dose adjustment is necessary to achieve plasma levels similar to those in young healthy subjects.

Clinical Trials

Depression

Moclobemide versus placebo
Clinical efficacy of moclobemide in the treatment of depression has been demonstrated in four randomised, placebo controlled, double-blind trials in a total of 475 patients (180 on moclobemide and 165 on placebo) using moclobemide doses of 200 - 600 mg/day. Three of these were multicentre trials performed predominantly in out-patients and one was a single-centre study performed predominantly in in-patients. Two of the studies compared moclobemide with placebo in parallel group design and two compared with placebo on one hand and with a TCA on the other. The duration of treatment was for 4-6 weeks.

The largest of these studies included 334 patients (117 on moclobemide, 110 on placebo). The mean final improvement in depression as assessed by score on the Hamilton Depression Scale (HAMD) was 48.7% for moclobemide and 31.9% for placebo treated patients. A final improvement of ≥ 50% on the HAMD occurred in 58% of moclobemide and 32% of placebo treated patients. The Clinical Global Impression (CGI) at the end of the 6 week treatment period was very good/good in 64.3% of patients for moclobemide and 32.1% for placebo treated patients. The efficacy of moclobemide versus placebo was statistically significant ($p < 0.001$) on all measured efficacy parameters.

Combining the investigator's global assessment of efficacy for all 4 studies, the efficacy was rated as very good/good in approximately 60% of patients who had received moclobemide and 30% of patients who had received placebo.

Moclobemide versus TCA's
Moclobemide was compared to TCA's in 19 double blind studies including a total of 1070 patients (542 on moclobemide and 528 on TCA). The mean moclobemide dose in these studies was 443 mg/day and score on the HAMD was reduced by ≥ 50% in 56% of patients. Moclobemide was found to have similar efficacy to the TCA's and the CGI was very good/good in 60.8% of moclobemide patients and 60.1% of patients treated with comparative TCA.

Moclobemide versus Irreversible MAOI's
Moclobemide was compared to the irreversible monoamine oxidase inhibitor (MAOI) tranylcypromine in 4 double blind studies with 159 patients (81 on moclobemide and 78 on tranylcypromine) using moclobemide doses of 150- 350 mg/day. The mean final reduction in HAMD score was 63% in the moclobemide group and 59% in the tranylcypromine group. Tolerance was more frequently rated as better in the moclobemide group and the number of patients who prematurely terminated was three times higher in the tranylcypromine group.

Moclobemide single daily versus divided daily dosing
This was a double blind, randomised, multicentre trial conducted in 189 patients for 6 weeks. The trial compared administration of single daily doses of moclobemide 450 mg (this could be increased up to 600 mg after 2 weeks) with this same daily dose given as three divided doses. The efficacies of the two dosing regimens were not found to be significantly different. Both the dosing regimens were found to be well tolerated although there was a significant increase in dizziness and a tendency for nausea, insomnia and headache in the once daily group.

Indications

Treatment of major depression.

Contraindications

Known hypersensitivity to the drug.
Acute confusional states.
Co-administration of selegiline (L-deprenyl) is contraindicated.
Co-administration of moclobemide with clomipramine should be avoided in clinical practice due to the risks of increased incidence of adverse effects.
Serotonin Syndrome (see Interactions with other medicines).

Precautions

Clinical Worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients. Antidepressants increased the risk compared to placebo of suicidality in children, adolescents, and young adults (aged 18-24 years) during initial treatment (generally the first one to two months) in short-term studies of major depression and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults over 24 years of age, and there was a reduction in risk with antidepressants compared to placebo in adults 65 years or older.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescents patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for Arima should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Patients with excitation or agitation as main clinical feature

Treatment of depressed patients with excitation or agitation as the main clinical feature may require addition of benzodiazepines.

Patients with schizophrenic symptoms

As is the case with other antidepressants, an exacerbation of schizophrenic symptoms is possible when depressive patients with schizophrenic or schizoaffective psychoses are treated. Therapy with long-term neuroleptics should, if possible, be maintained in such patients.

Dietary precaution

Treatment with moclobemide does not necessitate dietary restrictions in patients with normal dietary habits. Hypertensive patients are advised to avoid large quantities of tyramine-rich food such as ripe cheese (see Interactions with other medicines).

Hypertensive reactions

There are theoretical pharmacological grounds for supposing that drugs that inhibit monoamine oxidase may provoke hypertensive reactions in patients with thyrotoxicosis or pheochromocytoma. In the absence of relevant experience with moclobemide, the drug should be prescribed with caution for patients in these groups.

Effects on ability to drive and operate machinery

Impairment of performance in activities requiring complete mental alertness (e.g. driving a motor vehicle) is generally not to be expected with Arima. The individual reaction should however be monitored during early treatment.

Carcinogenicity, Mutagenicity, Impairment of Fertility

There was no evidence of carcinogenic effects following dietary administration of moclobemide to mice for 18 months at 250 mg/kg/day (750 mg/m^2/day) or to rats for 24 months at 225 mg/kg/day (1350 mg/m^2/day), doses which are 2 to 3 times the maximum recommended human dose calculated on a surface area basis.

Moclobemide was not genotoxic in assays for gene mutation, chromosomal damage or DNA damage.

There were no adverse effects on the fertility of rats receiving oral moclobemide 100 mg/kg/day (600 mg/m^2/day), a dose slightly more than the maximum recommended human dose calculated on a surface area basis.

Use in Pregnancy (Category B3)

Moclobemide and two of its metabolites were found in the amniotic fluid of pregnant rats 5 hours after dosing. Moclobemide lacked teratogenic activity in rats and rabbits at respective oral doses of 200 mg/kg/day (1200 mg/m^2/day) and 100 mg/kg/day (1100 mg/m^2/day), doses which are 2 to 3 times the maximum recommended human dose calculated on a surface area basis. However, there are no data on safety in human pregnancy and careful evaluation of the potential benefit and hazards to the mother and fetus should precede administration to pregnant women.

Use in Lactation

Although only a small amount of moclobemide passes into breast milk (approximately 1/30th of the adult dose), the benefits of continuing drug therapy for the breastfeeding mother should be weighed against possible risks to the child.

Use in Children and Adolescents (< 18 years)

The safety and efficacy of Arima for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Arima should not be used in this age group for the treatment of depression or other psychiatric disorders.

Interactions with other medicines

Selegiline
Co-administration of moclobemide with selegiline is contraindicated due to the relative loss of selectivity if both monoamine oxidase A and B are inhibited.

Selective serotonin reuptake inhibitors (SSRIs), Tricyclic Antidepressants (TCAs), Serotonin Syndrome and Washout Periods
Due to the possibility of development of Serotonin Syndrome, moclobemide should not be administered concomitantly with selective serotonin reuptake inhibitors or tricyclic antidepressants. This possibility increases with increasing dose and fatalities have occurred where one or more of these drugs have been ingested in overdose (see Overdosage).

There are limited data (ie small clinical pharmacology studies and post marketing reports) to support the safety of changing from low to moderate doses of serotonin re-uptake inhibitors to moclobemide 300 mg/day by ceasing the SSRI on one day and starting moclobemide on the next. In one study, 18 healthy subjects were changed from moclobemide 300 mg on day one to fluoxetine 40 mg/day for the next 7 days then fluoxetine 20mg/day for a further 7 days. On day 16, subjects were randomised to receive, in addition to fluoxetine 20 mg/day, moclobemide in ascending doses from 100 mg to 600 mg or placebo, for the next 8 days. On day 24, all patients received 300 mg moclobemide. There were no differences in the adverse reactions reported between the two groups, although the power of the study to detect clinically significant interactions is limited, given the number of subjects and the dose of moclobemide used. Caution is, however, recommended and the dose of moclobemide should be held at 300 mg/ day for the first week. Particular attention should also be given to the patient's medical history and concomitant therapy with other psychotropic drugs known to interact with or facilitate 5-HT functions.

Similarly, there are limited data to support the safety of changing from low to moderate doses of tricyclic antidepressants, for example 150 mg or less of amitriptyline to moclobemide 300 mg per day by ceasing the tricyclic antidepressant one day and starting Arima the next. The patient should be seen again soon after the changeover and progress monitored appropriately. The dose of moclobemide should be maintained at 300 mg/day for the first week.

Tyramine
In animal experiments it has been shown that the pressor effects of tyramine are less with moclobemide than with other inhibitors of monoamine oxidase. Results from studies in man showed that when tyramine is administered I.V. or orally under pharmacological conditions by using a provocative model, moclobemide leads to a slight and short-lasting potentiation of the tyramine pressor effect. The

potentiation of the pressor effect was even lower or did not occur when tyramine was mixed with a meal. A high protein or fat content meal further reduced the potentiation. In human studies it was demonstrated that up to 100 mg tyramine, corresponding to 1,000 g to 2,000 g mild or 200 g strong cheese, or to 70 g Marmite yeast extract, can safely be ingested during chronic treatment with three times 200 mg per day moclobemide post-prandially. Thus an interaction with tyramine rich foods is of no clinical importance during moclobemide treatment under normal conditions and moclobemide taken at the end of a meal. Neither age nor depression influences the interaction.

Dextromethorphan
Co-administration of moclobemide and dextromethorphan has occurred extensively in practice with in the vast majority of cases no reports of interaction. There have however been a few reports of possible central nervous system related adverse events such as giddiness, light headedness and agitation with concurrent administration.

Serotonin Agonists
Some serotonin agonists are metabolised predominantly by monoamine oxidase A and may need to be avoided or have their dosage reduced if administered concomitantly with moclobemide.

Pethidine
High dose studies in animals have demonstrated some potentiation of analgesic effect and increased restlessness with concomitant administration of pethidine and moclobemide. Concomitant administration of pethidine and moclobemide should be avoided or carried out only with caution.

Phenprocoumon
Concomitant administration of moclobemide, 200 mg three times per day, did not influence the parameters of blood coagulation controlled by phenprocoumon. No data are available regarding warfarin and moclobemide.

Digoxin
Concomitant administration of moclobemide to elderly patients under chronic digoxin treatment produced no significant changes in the digoxin plasma levels. There were no additional ECG disturbances, particularly no arrhythmias or conductance disturbances. Vital signs and laboratory parameters were also unaltered. The combination of moclobemide with metoprolol, nifedipine or hydrochlorothiazide, in patients stable on their antihypertensive treatment, was well tolerated and in particular there were no orthostatic reactions. The therapeutic benefits of nifedipine and hydrochlorothiazide were not influenced by moclobemide. The combination of moclobemide and metoprolol led to an additional BP reduction of 10 to 15 mmHg (systolic) and 5 to 10 mmHg (diastolic). The mechanism underlying this effect is not clear. In normotensive subjects moclobemide had no effect on BP.

Sympathomimetic amines
Possible undesired interactions between moclobemide and directly acting sympathomimetic amines were investigated in healthy subjects. Phenylephrine (PE) reactivity was investigated by infusion of increasing PE doses before and after moclobemide (100 mg single; 200 mg single; 100 mg three times per day for one week; 200 mg three times per day for three weeks) administration. After the three lowest doses, PE reactivity remained unchanged. After chronic administration of the highest dose there was a slight increase by 1.8 of the sensitivity factor in only four out of the six subjects, in the other two it was unchanged. Thus only after repeated administration of the high therapeutic doses of 200 mg three times per day moclobemide could a slight interaction be observed. PE was given intravenously, but in general it will be used as a nasal decongestant. Recommended use in these indications will be unlikely to result in concentrations of PE which cause relevant BP increases.

Cimetidine
A pharmacokinetic interaction (reduced moclobemide clearance) occurred in healthy subjects with combined administration of moclobemide and cimetidine. Thus if moclobemide treatment is initiated in a patient pre-treated with cimetidine the lowest dose should be given initially. If cimetidine has to be given after initiation of moclobemide treatment, it may be necessary to lower the moclobemide dose by 50% and to adjust according to clinical requirement.

Alcohol
Concomitant moclobemide administration did not further reduce performance in subjects with a blood content of alcohol distinctly reducing performance. Also in elderly subjects there was no additional influence at therapeutic doses.

Oral Contraceptives
The hormone levels (FSH, LH, oestradiol and progesterone) were not altered when moclobemide was administered concomitantly with combined contraceptives.

Effects on Laboratory Tests

Moclobemide does not affect laboratory tests.

Adverse Effects

Arima is usually well tolerated. No adverse event occurred with an increased frequency of more than 5% compared to placebo. The following transient effects have been observed: sleep disturbances, dizziness, nausea, and headache. In very rare cases confusional states have been observed, but these rapidly disappeared on discontinuation of therapy.

Table 1. Adverse effects reported in clinical trials at an incidence of >1% where causality is at least possibly related to moclobemide

Organ System	Adverse Event	Moclobemide (%)	Placebo (%)
Central Nervous System	Insomnia	7.4	4.8
	Dizziness	9.8	8.1
	Anxiety	4.6	2.2
	Restlessness	4.2	2.6
Gastrointestinal	Nausea	9.5	4.8
	Constipation	5.3	3.3
	Diarrhoea	3.2	1.1
Anticholinergic	Dry mouth	13	10.6

Other adverse events with an incidence of <1% in clinical studies, or reported in post-marketing surveillance are as follows:

Psychiatric: Difficulties falling asleep, nightmares/dreams, hallucinations, memory disturbances, confusion, disorientation, delusions, increased depression, excitation/irritability, hypomanic symptoms, aggressive behaviour, apathy, tension.

Central and Peripheral Nervous System: Migraine, extrapyramidal effects, tinnitus, paraesthesia, dysarthria.

Gastrointestinal: Heartburn, gastritis, meteorism, indigestion.

Cardiovascular: Hypertension, bradycardia, extrasystoles, angina/chest pain, phlebetic symptoms, flushing.

Dermatological/Mucocutaneous: Exanthema/rash, allergic skin reaction, itching, gingivitis, stomatitis, dry skin, conjunctivitis, pruritus, urticaria.

Genitourinary: Disturbances of micturition (dysuria, polyuria, tenesmus), metrorrhagia, prolonged menstruation.

Miscellaneous: General malaise, skeletal/muscular pain, altered taste sensations, hot flushes/cold sensation, photopsia, dyspnoea, visual disturbances.

Dosage and Administration

Major depression
Arima therapy should be initiated in two divided daily doses. The recommended initial daily dose is 300 or 450 mg. The recommended dose range is 300 - 600 mg/day. Arima should be taken after meals.

Dosage in the elderly
No dosage adjustments are necessary in elderly patients.

Dosage in patients with impaired renal function
Single dose pharmacokinetic data suggest that no dosage adjustment may be required in patients with reduced renal function. However, multiple dose studies with moclobemide have not been performed in patients with renal dysfunction; therefore, Arima should be used with caution in this patient population. In normal volunteers, the absolute bioavailability almost doubles following multiple dosing as compared to a single dose.

Dosage in patients with impaired hepatic function
In patients with severely impaired hepatic metabolism, the daily dose of Arima should be reduced to half or one third of the dose to reach the usual plasma level.

Overdosage

The highest reported overdose is 20.55g. The usual signs of overdose with moclobemide alone are nausea, vomiting, drowsiness, disorientation, slurred speech, amnesia, reduced reflexes, agitation, hypertension and convulsions.

As with other antidepressants, combination overdoses of moclobemide and other antidepressants, alcohol and other drugs can be life threatening. Fatalities have been reported in combination overdoses. Patients should be hospitalised and closely monitored so that appropriate treatment can be given. Serotonin syndrome symptoms (hypertension, spasm, altered consciousness) have been reported with mixed overdoses with clomipramine or selective serotonin reuptake inhibitors.

Management of overdose should include monitoring of vital signs and consideration of other agents ingested in multiple overdoses.

Contact the Poisons Information Centre on 131126 (Australia) for advice on management of overdosage.

Presentation and Storage Conditions

Arima 150 Moclobemide 150 mg, oval, cylindrical, pale yellow, film-coated, scored, marked MOC 150; blister pack of 60 tablets.

Arima 300 Moclobemide 300 mg, oval, cylindrical, white to yellowish white, film-coated, scored, marked MOC 300; blister pack of 60 tablets.

Arima should be stored below 30°C. The tablets should not be used after the expiry date imprinted on the blister pack and carton.

Poison Schedule of the Medicine

S4 (Prescription Only Medicine)

Name and Address of the Sponsor

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Date of Approval

Approved by the Therapeutic Goods Administration on 7 April 2005.
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